Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**tenofovir disoproxil fumarate**	**entecavir**	**adefovir**
Brand Name	Viread®, generics	Baraclude®, generics	Hepsera®, Apo-adefovir
Dosage Form(s)	300 mg tablet	0.5 mg tablet	10 mg tablet
Manufacturer	Gilead Sciences Canada Inc., other generic manufacturers	Bristol Myers Squibb Canada, other generic manufacturers	Gilead Sciences Inc., Apotex Inc.
Submission Type	**Modification of Criteria**		
Use Reviewed	For chronic hepatitis B (CHB)		
Common Drug Review (CDR)	No, CDR did not review		
Drug Benefit Council (DBC)	DBC met on July 9, 2018. DBC considered various inputs including: the final reviews completed by the CDR on October 18, 2007 (for adefovir), November 28, 2007 (for entecavir) and March 18, 2009 (for tenofovir disoproxil fumarate), which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC considered earlier DBC reviews from November 29, 2007 (adefovir and entecavir) and April 27, 2009 (tenofovir disoproxil fumarate), as well as three documents published September 28, 2015 by the Ontario Drug Policy Research Network (ODPRN): an Environmental Scan and Local/Historical Context of Treatments for CHB; a Pharmacoeconomics Unit document; and a Treatment for CHB: Systematic Review and Network Meta-Analysis document. The DBC considered the Canadian Association for the Study of Liver Disease (CASL) 2012 guidelines (the 2018 update has not yet been published), the National Institute for Health and Care Excellence (NICE) June 2013 guidelines (updated in 2017), the American Association for the Study of Liver Diseases (AASLD) 2018 guidelines, the European Association for the Study of the Liver (EASL) 2017 guidelines, and the Asia-Pacific Association for the Study of the Liver (APASL) 2015 guidelines.The DBC considered Clinical Practice Review Reports from three specialists, as well as a Budget Impact Assessment.		
Drug Coverage Decision	**Limited Coverage Benefit. Access the tenofovir disoproxil fumarate and entecavir modified criteria from www.gov.bc.ca/pharmacarespecialauthority** **Non-Benefit** for adefovir		
Date	November 27, 2018		
Reason(s)	**Drug coverage decision is consistent with the DBC recommendation.** • The Ministry is reviewing the coverage for tenofovir disoproxil fumarate and entecavir to address the unmet needs for a drug with a higher effectiveness and a lower risk of resistance as first-line treatment options for CHB. • Tenofovir disoproxil fumarate and entecavir are the most effective treatment for CHB in suppressing the hepatitis B virus, as well as having the lowest rate of drug resistance. • Adefovir is rarely used due to its low potency and higher rate of drug resistance than tenofovir disoproxil fumarate. • Effective **November 27, 2018**, PharmaCare is expanding the criteria for tenofovir disoproxil		

	fumarate and entecavir to provide coverage for treatment-naive patients with CHB, regardless of the severity of their disease. • Also, effective **November 27, 2018**, no new Special Authority (SA) requests for adefovir will be approved for CHB. Patients with existing SA approval for adefovir have been automatically granted approval for tenofovir disoproxil fumarate and will have until May 29, 2019 to transition to tenofovir disoproxil fumarate.
Other Information	None

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Common Drug Review (CDR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit the The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Chronic Hepatitis B Therapeutic Review

Tenofovir disoproxil fumarate(Viread® and generics)
Entecavir (Baraclude® and generics)
Adefovir (Hepsera® and generics)

Description:

Drug review of **tenofovir disoproxil fumarate (Viread® and generics), entecavir (Baraclude® and generics)** and **adefovir (Hepsera® and generics)** for the following Health Canada approved indications:

For the treatment of chronic hepatitis B.

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on October 18, 2007 (for adefovir), November 28, 2007 (for entecavir) and March 18, 2009 (for tenofovir), which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC).

The DBC also considered earlier DBC reviews from November 29, 2007 (adefovir and entecavir) and April 27, 2009 (tenofovir), as well as three documents published September 28, 2015 by the Ontario Drug Policy Research Network (ODPRN): an Environmental Scan and Local/Historical Context of Treatments for Chronic Hepatitis B; a Pharmacoeconomics Unit document; and a Treatment for Chronic Hepatitis B: Systematic Review and Network Meta-Analysis document.

The DBC considered the Canadian Association for the Study of Liver Disease (CASL) 2012 guidelines (the 2018 update has not yet been published), the National Institute for Health and Care Excellence (NICE) June 2013 guidelines (updated in 2017), the American Association for the Study of Liver Diseases (AASLD) 2018 guidelines, the European Association for the Study of the Liver (EASL) 2017 guidelines, and the Asia-Pacific Association for the Study of the Liver (APASL) 2015 guidelines.

The DBC considered Clinical Practice Review Reports from three specialists, as well as a Budget Impact Assessment.

The Ministry currently provides coverage for the following treatments for CHB:

- Lamivudine is listed as first-line treatment for treatment-naïve patients with or without compensated cirrhosis.
- Interferon is listed as first-line treatment for treatment-naïve patients without compensated cirrhosis.
- Tenofovir disoproxil fumarate and entecavir are listed in combination as a first-line therapy for treatment-naïve patients with compensated cirrhosis.
- Adefovir is listed alone or in combination with lamivudine for patients with lamivudine resistance with or without compensated cirrhosis.
- Tenofovir disoproxil fumarate is listed for patients with lamivudine resistance and/or who are adefovir-experienced with persistent viremia, with or without compensated cirrhosis.

Questions for Consideration (DBC)

1. Based on the evidence provided, should the British Columbia Ministry of Health (the Ministry) expand the PharmaCare coverage of tenofovir disoproxil fumarate to make it the first-line chronic hepatitis B (CHB) therapy for treatment-naïve patients without compensated cirrhosis?
2. Based on the evidence provided, should the Ministry expand the PharmaCare coverage of tenofovir disoproxil fumarate and entecavir to make it the first-line CHB therapy for treatment-naïve patients without compensated cirrhosis?
3. Based on the evidence provided, should the Ministry de-list adefovir for the treatment of CHB?

Dosage Forms:

- Tenofovir disoproxil fumarate (Viread, generics) is available in 300 mg tablet.
- Entecavir (Baraclude, generics) is available in 0.5 mg and 0.05 mg/mL tablet and solution.
- Adefovir (Hepsera, generics) is available in 10 mg tablet.

Recommendations:

1. The Drug Benefit Council (DBC) recommends that the Ministry provide coverage for either:
    a. Tenofovir disoproxil fumarate as a first-line benefit for the treatment of CHB for treatment-naïve patients without compensated cirrhosis; **OR**
    b. Tenofovir disoproxil fumarate and entacavir as first-line benefits for the treatment of CHB in treatment-naïve patients without compensated cirrhosis.

2. Adefovir should be **delisted** as a benefit for the treatment of CHB.
    a. Patients who are currently taking adefovir alone should be switched to tenofovir and entecavir.

Of Note:

- The DBC recommends the Ministry should review lamivudine for possible delisting as a benefit and return to the DBC for consideration.

Reasons for the Recommendation:

1. Summary

- In naïve patients with compensated cirrhosis, tenofovir and entecavir should be used as first-line agents because they have the highest efficacy in terms of virologic response and alanine aminotransferase (ALT) normalization and lowest rates of resistance (0% for tenofovir over three years and 1-2% for entecavir over five years).
- Because of its lower efficacy and higher rate of drug resistance, adefovir should not be a first-line treatment and should only be used in combination with other agents as a second-line treatment.
- Because of its lower efficacy and highest rates of resistance (70-80% over five years), lamivudine should not be used.
- Lamivudine, entecavir, adefovir and tenofovir are all now available as generics and are thus priced significantly lower than they were when first listed as benefits.

2. Clinical Efficacy

- The DBC focused the discussion on the Treatment for Chronic Hepatitis B Systematic Review and Network Meta-Analysis prepared by the ODPRN, which estimated pooled effectiveness and safety data from randomized controlled (RCT) studies on the following outcomes: efficacy for hepatitis B e-antigen (HBeAg) positive patients (virologic response, ALT normalization, HBeAg loss, HBeAg seroconversion, and Hepatitis B surface antigen loss); efficacy for HBeAg negative patients (virologic response and ALT normalization); and serious adverse events, any adverse events, and withdrawal due to adverse events.
- The ODPRN systematic review and network meta-analysis concluded the following:
  - In terms of virologic response and ALT normalization for HBeAg positive patients, tenofovir is the most effective treatment followed by entecavir.
  - In terms of HBeAg loss and HBeAg seroconversion, pegylated interferon is the most effective treatment.
  - In terms of Hepatitis B surface antigen (HBsAg) loss, pegylated interferon is the most effective treatment followed by tenofovir.
  - In terms of virologic response and ALT normalization for HBeAg negative patients, tenofovir is also the most effective treatment, followed by adefovir and entecavir.
- Four of the five major guidelines recommend tenofovir or entecavir as first-line for treatment naïve patients with CHB. Tenofovir is recommended as first-line for lamivudine-resistant patients in all guidelines.
- The ODPRN systematic review found that the prevalence of drug resistance varies across treatments, with the highest prevalence found with lamivudine (70-80% within five years), the next highest with adefovir (approximately 30% of patients at five years for HBeAg-negative patients), and lowest with entecavir (approximately 1-2% within six years) and tenofovir (0% during the initial three-year trials).
- Cross-resistance is also present in the drugs belonging to the same class, or in drugs belonging to difference classes. Approximately 51% of lamivudine-refractory patients develop entecavir resistance in 5 years.

3. Safety

- The ODPRN systematic review found that pegylated interferon was associated with a significantly higher number of serious adverse events than lamivudine, telbivudine, and entecavir. The likelihood of any adverse event was also significantly higher in studies involving pegylated interferon than placebo, lamivudine, adefovir, telbivudine, tenofovir and entecavir. Withdrawal due to adverse events was significantly less frequent in entecavir compared to lamivudine and pegylated interferon.
- Other than these, there was no significant difference was found between the oral agents in terms of safety.

4. Economic Considerations

- Lamivudine, entecavir, adefovir and tenofovir are all now available as generics and are thus priced significantly lower than they were when first listed as benefits. The annual cost ranges from approximately $1,391 for lamivudine to $7,402 for adefovir).
- The interferon-based regimens do not have generic options and are significantly more expensive than the other treatments (from approximately $5,834 to $19,554 annually, depending on genotype).
- When these therapies are used in combination (e.g. tenofovir and entecavir, or lamivudine and adefovir) the annual cost increases significantly, although the annual cost is still less than the interferon-based regimens.
- The ODPRN Pharmacoeconomics Unit document reviewed available Canadian studies and suggested that tenofovir may be cost effective as a first line therapy, albeit when limited to certain subgroups.

5. Of Note

- The DBC did not solicit patient input for this review.